Environmental enrichment reverses tyrosine kinase inhibitor-mediated impairment through BDNF-TrkB pathway

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Exposure to an enriched environment (EE) has neuroprotective benefits and improves recovery from brain injury due to, among other, increased neurotrophic factor expression. Through these neurotrophins, important cortical and hippocampal changes occur. Vandetanib acts as a tyrosine kinase inhibitor of cell receptors, among others, the vascular endothelial growth factor receptor (VEGFR). Our aim was to investigate the effectiveness of EE counteracting cognitive and cellular effects after tyrosine kinase receptor blockade. Animals were reared under standard laboratory condition or EE; both groups received vandetanib or vehicle. Visuospatial learning was tested with Morris water maze. Neuronal, interneuronal, and vascular densities were measured by inmunohistochemistry and histochemistry techniques. Quantifications were performed in the hippocampus and in the visual cortex. Brain-derived neurotrophic factor (BDNF), tyrosine kinase B receptor (TrkB), Akt, and Erk were measured by Western blot technique. Vandetanib produces a significant decrease in vascular and neuronal densities and reduction in the expression of molecules involved in survival and proliferation processes such as phospho-Akt/Akt and phospho- Erk/Erk. These results correlated to a cognitive impairment in visuospatial test. On the other hand, animals reared in an EE are able to reverse the negative effects, activating PI3K-AKT and MAP kinase pathways mediated by BDNF-TrkB binding. Present results provide novel and consistent evidences about the usefulness of living in EE as a strategy to improve deleterious effects of blocking neurotrophic pathways by vandetanib and the notable role of the BDNF-TrkB pathway to balance the neurovascular unit and cognitive effects.

Enriched environment

Hippocampus

Neuroprotection

Neurotrophins

Tyrosine kinase inhibitor

Visual cortex

brain derived neurotrophic factor

brain derived neurotrophic factor receptor

calbindin

calretinin

mitogen activated protein kinase

parvalbumin

protein kinase B

protein tyrosine kinase inhibitor

somatostatin

vandetanib

Bdnf protein, rat

brain derived neurotrophic factor

brain derived neurotrophic factor receptor

protein kinase inhibitor

protein tyrosine kinase

TrkB protein, rat

animal cell

animal experiment

animal tissue

Article

brain region

cell density

cell proliferation

cell survival

cognition

cognitive defect

controlled study

dentate gyrus

environmental enrichment

hippocampus

immunohistochemistry

MAPK signaling

Morris water maze test

nerve cell

nonhuman

protein binding

protein function

quantitative analysis

rat

signal transduction

spatial learning

stereology

visual cortex

Western blotting

animal

antagonists and inhibitors

drug effect

environment

Long Evans rat

metabolism

physiology

signal transduction

Animals

Brain-Derived Neurotrophic Factor

Environment

Protein Kinase Inhibitors

Protein-Tyrosine Kinases

Rats

Rats, Long-Evans

Receptor, trkB

Signal Transduction